**Application of Physiologically Based Toxicokinetic/Toxicodynamic Models in Assessing Neurodevelopmental Toxicity of Susceptible Populations**

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**Environmental Issues**

How can physiologically based toxicokinetic/toxicodynamic **(**PBTK/TD) models be used to assess the impact of neurodevelopmental toxicity during different life stages? What framework can be developed for incorporating toxicokinetic (TK) and toxicodynamic (TD) processes into the risk assessments of children?

**Research**

This collaborative study focused on how PBTK/TD models are particularly useful when assessing the impact of neurodevelopmental toxicants in sensitive populations, such as children. Specifically, modeling approaches were developed with researchers in the ORD and the University of Washington that can quantitatively address critical issues in neurodevelopmental processes based on windows of susceptibility, inter- and intra-species variability, mode of action, and extrapolation of toxicity data. Understanding the kinetics and dynamics of neurodevelopmental impacts in one species can help identify the potential dose range(s), time(s), and target tissue(s) in humans. The quantitative consideration of kinetic and dynamic processes provides an understanding of the response as an integrated process and allows for the evaluation of dose-dependent differences in mechanisms of toxicity. In addition, PBTK/TD models facilitate the identification of critical rate-limiting steps that may control subsequent dynamic processes and which may also be susceptible to chemical perturbation.

In this research, case studies of the developmental toxicity of ethanol and methyl mercury have demonstrated the utility of linking the PBTK/TD models to allow the assessment of dose, temporal, and tissue-specific effects. For ethanol, a dynamic model was developed that could predict the relative contribution of the chemical-induced changes in apoptosis versus proliferation. Research results suggest that early exposures to this chemical, and the subsequent impacts on proliferation, may account for significant proportions of observed reductions in cell number during neurodevelopment. In the methyl mercury model, windows of susceptibility, mode or mechanism of action, *in vitro* and *in vivo* issues, and exposure conditions were considered. Findings indicated that the effects on cell proliferation did not affect cell cycle kinetics up to concentrations of 3 ppm (rat embryonic tissues), in contrast to previous studies in mice. Equally important, the research suggests important species differences in toxicodynamic sensitivity.

**Impact/Outcomes**

This research program reduces uncertainty in risk assessment by

• Developing improved TK/TD methods for evaluating potential risks to children; critically important sensitive subpopulation

• Developing a new framework based on biologically based dose–response models for assessing children's health

• Identifying future research needs to improve future risk assessments and reduce children's risks to environmental toxicants.